



# Possible adverse drug events leading to hospital admission in a Brazilian teaching hospital

Fabiana Rossi Varallo,<sup>I</sup> Helaine Carneiro Capucho,<sup>II</sup> Cleópatra da Silva Planeta,<sup>III</sup> Patrícia de Carvalho Mastroianni<sup>IV</sup>

<sup>I</sup>Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), School of Pharmaceutical Sciences, Department of Drugs and Medications, Araraquara/SP, Brazil. <sup>II</sup>Ministério da Saúde, Comissão Nacional de Incorporação de Tecnologias, Brasília/DF, Brazil. <sup>III</sup>Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), School of Pharmaceutical Sciences, Department of Natural Active Principles and Toxicology, Araraquara/SP, Brazil. <sup>IV</sup>Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), School of Pharmaceutical Sciences, Department of Drugs and Medications, Araraquara/SP, Brazil.

**OBJECTIVES:** Drug safety problems can lead to hospital admission. In Brazil, the prevalence of hospitalization due to adverse drug events is unknown. This study aims to estimate the prevalence of hospitalization due to adverse drug events and to identify the drugs, the adverse drug events, and the risk factors associated with hospital admissions.

**METHOD:** A cross-sectional study was performed in the internal medicine ward of a teaching hospital in São Paulo State, Brazil, from August to December 2008. All patients aged  $\geq 18$  years with a length of stay  $\geq 24$  hours were interviewed about the drugs used prior to hospital admission and their symptoms/complaints/causes of hospitalization.

**RESULTS:** In total, 248 patients were considered eligible. The prevalence of hospitalization due to potential adverse drug events in the ward was 46.4%. Overprescribed drugs and those indicated for prophylactic treatments were frequently associated with possible adverse drug events. Frequently reported symptoms were breathlessness (15.2%), fatigue (12.3%), and chest pain (9.0%). Polypharmacy was a risk factor for the occurrence of possible adverse drug events.

**CONCLUSION:** Possible adverse drug events led to hospitalization in a high-complexity hospital, mainly in polymedicated patients. The clinical outcomes of adverse drug events are nonspecific, which delays treatment, hinders causality analysis, and contributes to the underreporting of cases.

**KEYWORDS:** Adverse Drug Reaction Reporting Systems; Product Surveillance; Postmarketing; Pharmacovigilance; Admitting Department; Hospital.

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E-mail: patriciamastroianni@yahoo.com.br

Tel.: 55 16 3301-6977

## ■ INTRODUCTION

Adverse drug events (ADEs) involve "harm caused by a drug or the inappropriate use of a drug" (1). ADEs can mimic diseases, decrease the confidence of patients in doctors, and delay both diagnosis and treatment (2). These events are responsible for up to 54% of hospital admissions (3), and 1.5% of them are fatal (2). Moreover, ADEs can increase the length of hospital stays by 2.9 days, raising hospital costs (4).

Factors that predispose a patient to ADEs are age (5,6), female gender (6), and polypharmacy (6,7). There is no consensus regarding alcohol consumption as a risk factor for the occurrence of an adverse drug reaction (8,9), which is a negative clinical outcome related to an ADE.

In Brazil, pharmacovigilance is recent, and there have been few studies assessing drug safety and ADE-related hospital admissions. This study aims to estimate the number of patients with symptoms consistent with a known ADE; to assess the likelihood that a drug caused an ADE; and to identify the drugs, the ADEs themselves, and the risk factors associated with hospitalization.

## ■ MATERIALS AND METHODS

A cross-sectional pilot study was performed in a general, public state teaching hospital in São Paulo State, Brazil, with 848 active beds.

All patients aged  $\geq 18$  years who agreed to participate by providing written informed consent; who had taken at least

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one drug before hospital admission; and who were admitted to the internal medicine ward (107 beds) from August 19 to December 19, 2008, met the inclusion criteria and were enrolled. The exclusion criteria were patients transferred from another hospital or ward; those with prescheduled surgery; those unable to communicate (intubated, in isolation, or mentally disoriented); and those with a hospital stay  $\leq 24$  hours, including patients in the emergency unit, who cannot be interviewed, and certain internal medicine patients who were admitted to the ward for rapid treatment with drugs whose use is restricted to hospital wards.

Employing a validated form (10), the investigator interviewed the subjects who met the inclusion criteria to collect the data. The instrument was designed to have three sections. The first section collected personal information regarding the patient, such as the initials of the name and sociodemographic characteristics (alcohol consumption, smoking habits, gender, and age group [elderly or not elderly]). This part also included data on patient hospital registration and bed and the dates and times of hospital admission and discharge. The second section addressed the personal history of drug treatment to identify the drugs administered prior to hospital admission and the complaints/reasons for hospitalization. The third section comprised questions that allowed the analysis of causal association by collecting data about the time relationship between drug use and the adverse event, the response to dechallenge (discontinuation of or decrease in dose), and the response to rechallenge (drug re-administration) and about competing causes of the ADEs (implying that the complaint reported by a patient was not related to drug use).

In addition, medical prescriptions brought by patients were consulted with the aim of confirming the pharmacotherapy prescribed by the family doctor. When medical prescriptions were not available but either patients or their caregivers noted that they were able to reply to all points raised on the form, without loss of information, medical records were not consulted. This approach was adopted due to a lack of information about the personal history of drug treatment performed at home in these documents. In cases in which the patients did not present their medical prescriptions and could not remember the drugs taken at home, medical records were consulted as a last source of data on drugs administered.

To determine whether the complaints/reasons for hospitalization reported by patients were expected ADEs (described in clinical trials) and to perform a causality assessment, the drug information sheets approved by the National Agency of Sanitary Surveillance (ANVISA) and monographs, such as those in DRUGDEX (MICROMEDEX® database), were consulted.

For the causality assessment, the algorithm of Naranjo (11) was employed. Causal association was performed by a pharmacist, based on the complaints reported by patients, the drugs used prior the hospitalization (second section of the instrument), and the questions raised in the algorithm of Naranjo (11) (third section of the instrument). When a likely connection between drug intake and the occurrence of a negative outcome was found, the drugs related to the ADE were classified according to the Anatomical Therapeutic Chemical (ATC) Code.

Data obtained from the interviews and the likelihood of ADE were expressed as frequencies and subjected to an

analysis of descriptive statistics. The chi-squared test was applied to the dichotomous variables age (elderly or not elderly), gender, ethanol consumption, and smoking habit to reveal statistically significant differences between patients who were possibly hospitalized due to an ADE and those who were admitted for other reasons. Patients aged  $\geq 60$  years were considered "elderly". Odds ratios (ORs) were calculated to analyze the association between dichotomous variables and the occurrence of ADEs. The Mann-Whitney test was used to assess the statistical significance of associations between the number of drugs (continuous variable with nonparametric distribution) and the risk of an ADE and between the length of stay (independent variable) and an ADE related to hospitalization. The intake of five or more drugs was considered polypharmacy (12).

To control for potential confounding factors and to determine independent associations between an ADE and its risk factors, multivariate logistic regression analysis was employed, with an ADE as the outcome and gender, age, ethanol consumption, smoking habit, the number of drugs used, and the length of stay as independent variables. In all tests, significance was accepted when  $p < 0.05$ .

## ■ RESULTS

During the study period, 1,180 patients were admitted to the internal medicine ward. Of these patients, 664 (56.3%) met the exclusion criteria, and 260 (22.0%) could not be interviewed. In total, 256 (21.7%) met the inclusion criteria. Seven patients did not remember the drugs taken at home, and this information was not found in medical records, and one patient withdrew his consent during data collection, so only 248 patients were considered eligible. Therefore, the prevalence of hospital admission due to a potential ADE was 46.4% (115/248).

Patients reported 178 ADEs. Six (3.4%) were classified as definite, 54 (30.3%) as probable, and 118 (66.3%) as possible. Frequently reported ADEs were breathlessness (15.2%), fatigue (12.3%), chest pain (9.0%), abdominal pain (8.9%), and hyperglycemia (5.6%).

By univariate analysis, ethanol consumption and polypharmacy were detected as a protective factor and a risk factor, respectively, for the occurrence of ADE (Table 1). However, in the multivariate regression analysis, only polypharmacy showed a significant influence on ADE occurrence. Furthermore, no significant difference was observed in the length of hospital stay for patients admitted due to an ADE (Table 1).

The therapeutic classes of the 10 drugs frequently associated with ADEs were cardiovascular, alimentary tract, and metabolism and blood and blood-forming organs (Table 2).

## ■ DISCUSSION

The prevalence of severe ADEs that might lead to hospital admission was found to be approximately one in two patients who had taken at least one drug prior to hospitalization. Severe ADEs are defined as causing hospitalization, being fatal or life-threatening, or resulting in significant changes in a patient's treatment (presumably thereby prolonging hospitalization) (13). Our findings corroborate the data of a systematic review (3) and can be used as an indicator of the need for a safety assessment of

**Table 1** - Frequency of ADEs identified according to potential risk factors in groups of patients admitted to the internal medicine ward (n = 248).

Variable	ADE		Univariate analysis		Logistic regression	
	No	Yes	OR raw	(95% CI)	OR adj.	(95% CI)
<b>Gender</b>						
Female	74 (49.3)	76 (50.7)	(a) 1.00	(0.9-2.6)	1.00	(0.77-2.32)
Male	59 (60.2)	39 (39.8)			1.34	
<b>Age</b>						
Not elderly	84 (56.0)	66 (44.0)	1.00	(0.8-2.1)	1.00	(0.66-1.93)
Elderly	49 (50.0)	49 (50.0)	1.30		1.13	
<b>Ethanol consumption</b>						
No	108 (50.7)	105 (49.3)	1.00	(0.2-0.9)*	1.00	(0.17-1.02)
Yes	25 (71.4)	10 (28.6)	0.40		0.42	
<b>Smoking habit</b>						
No	116 (54.2)	98 (45.8)	1.00	(0.6-2.4)	1.00	(0.91-4.73)
Yes	17 (50.0)	17 (50.0)	1.20		2.07	
<b>Number of drugs</b>						
Median	4	5	(p:U) 0.006+		1.14	(1.03-1.26) **
Minimum	1	1				
Maximum	13	14				
<b>Length of stay (days)</b>						
Median	8	8	0.572		1.00	(0.98-1.02)
Minimum	1	1				
Maximum	147	81				

OR raw: Odds ratio, 95% CI = 95% confidence interval;

OR adj.: Adjusted odds ratio; 95% CI = 95% confidence interval.

\*Significant: patients who reported ethanol consumption were less likely to experience an ADE (chi-squared: p&lt;0.05).

+ Significant: a higher number of drugs used increased the occurrence of an ADE (chi-squared: p&lt;0.05).

\*\*Significant: the odds of an ADE increased by 14% when one more drug was administered.

(a) OR = 1.00 indicates the group used as a reference.

the pharmacotherapies prescribed at the primary and secondary health care levels, for pharmacotherapeutic follow-up of patients, and for the development of risk minimization plans to allow the early recognition of drug-related problems (DRPs) to avoid inappropriate prescribing/health care and to improve patient safety. Such measures could contribute to the reduction of hospitalization related to DRPs and hospital costs (3).

Most of the hospital admissions possibly arising from ADEs that were detected in the present study were associated with cardiovascular drugs. This finding was expected because it was also observed by Kongkaew et al. (7). Salicylates are often prescribed to patients with hypertension and diabetes to avoid cardiovascular complications (14). However, acetylsalicylic acid has been associated with hospital admissions arising from ADEs (5). Therefore, patients who take cardiovascular and antithrombotic drugs should be included and prioritized in pharmaceutical care services to assess the safety of the prophylactic treatment and to decrease the prevalence of hospitalizations due to DRPs.

Omeprazole was the main drug responsible for hospitalizations related to symptoms that were consistent with a known ADE. In Brazil, the prescription of and self-medication with omeprazole are common among patients treated with polypharmacy to prevent disorders of the digestive tract. Therefore, the high frequency of omeprazole-related possible ADEs was expected due to its overprescription. However, this finding does not necessarily imply a real causal relationship because the clinical manifestations of the possible ADEs reported by patients may have been symptoms of undetected disorders, such as ulcer and reflux.

Clinical manifestations of ADEs were nonspecific, hindering their detection and leading to overestimation in the causality assessment. Overestimates most likely occur because few professionals are qualified to perform activities related to post-commercialization surveillance, given that it is only a recent practice in Brazil. This surveillance began in 2001 with the project of Sentry Hospitals. The main aim of the network of Sentry Hospitals is to establish a culture of ADE reporting to quantitatively increase the amount of information regarding DRPs. In 2013, the Health Ministry established the National Program of Patient Safety (15), which may contribute to the assessment of ADE causality because this program encourages the discussion of risk management among the members of multidisciplinary teams involved in health care, improving the quality of information.

The algorithm of Naranjo also limits the assessment of the likelihood of ADEs because this instrument was developed for controlled clinical trials whose risk management and health care are different from those of the participants enrolled in the present study. Thus, the algorithm includes several clinical practices that are not frequently conducted (for example, laboratory tests to check the plasma concentrations of most drugs are not performed, reexposure of the patient to the drugs is rarely conducted, and the administration of placebo is considered to be an ethical issue and is strongly discouraged). Thus, withdrawal of the drug with a consequent improvement of the patient is the only parameter used to assess causality when other conditions do not explain a patient's symptoms (16).

Moreover, it is important to stress that the strength of causal association depends on the quantity and quality of information collected, which should be revised as more information becomes available (1). However, because the

**Table 2** - Frequency of the 10 drugs most commonly taken by patients prior to admission to the internal medicine ward, as reported at hospital admission, along with their ATC codes, the ADEs identified, and an assessment of causality using the Naranjo algorithm.

Drug	N	ATC code*	ADE related to hospital admission	Causality assessment
Omeprazole	23	A	Fatigue (3), abdominal pain (1), chest pain (2), cough (4), diarrhea (1), edema (1), anemia (1) Abdominal pain (5), bronchospasm (4), fatigue (4), chest pain (2), back pain (2), vomiting (1), edema (1), diarrhea (1), hepatotoxicity (1), leg pain (1), fever (1), tachycardia (1)	Probable Possible
Captopril	20	C	Cough (3), bronchospasm (1), tachycardia (1) Bronchospasm (7), angina (6), diarrhea (3), cough (1), tachycardia (1), gastrointestinal ulcer (1), fever (1), abdominal pain (1), vomiting (1), hypoglycemia (1), somnolence (1), hypotension (1)	Probable Possible
Insulin	20	A	Insulin resistance (3), bronchospasm (2), chest pain (1), diarrhea (1), anemia (1), edema (1)	Probable
Acetylsalicylic acid	17	B	Insulin resistance (5), bronchospasm (3), chest pain (4), diarrhea (1), hypoglycemia (1), Bronchospasm (3), angina (1), Bronchospasm (11), angina (2), hypertension (1), gastrointestinal ulcer (1)	Possible Probable Possible
Furosemide	14	C	Abdominal pain (2), diarrhea (1), anemia (1), fever (1) Abdominal pain (2), dizziness (3), diarrhea (2), nausea (1), erythema (1), hyperglycemia (1), fever (1)	Probable Possible
Propranolol	10	C	Fatigue (1), bronchospasm (2), angina (1), diarrhea (1), pruritus (1) Fatigue (5), bronchospasm (3), angina (1), vomiting (1), gastrointestinal disorder (1)	Probable Possible
Simvastatin	10	C	Angina (2), dizziness (2), abdominal pain (1) Angina (2), dizziness (2), proteinuria (2), fatigue (2), abdominal pain (1), constipation (1)	Probable Possible
Carvedilol	8	C	Bronchospasm (1), edema (1), cough (1), syncope (1), Bronchospasm (3), edema (2), fatigue (2), angina (1), erythema (1)	Probable Possible
Digoxin	8	C	Poisoning by glycoside cardiac (1), Poisoning by glycoside cardiac (1), dizziness (1), abdominal pain (1), headache (1) Fatigue (2), dizziness (1),	Definite Probable Possible
Enalapril	7	C	Dizziness (1), paresthesia (1) Dizziness (1), hyperglycemia (2), fatigue (1), anemia (1) Myalgia (1), cough (1)	Definite Probable Possible

\*ATC codes: A = alimentary tract and metabolism; B = blood and blood-forming organs; C = cardiovascular system.

data collection depended on the memory of the subjects enrolled in the study and given the lack of information regarding pharmacotherapeutics taken at home (including adherence and self-medication) and the difficulty in discussing the cases with the family physicians of the patients (they were not linked to the institution), the assessment of ADE likelihood was impaired. Nevertheless, the report of any suspicion of an ADE is encouraged by ANVISA. Therefore, even when the Naranjo algorithm indicated a weak likelihood (possible) that a drug was associated with the complaints reported, we included this information in our findings.

Polypharmacy was the only risk factor for the occurrence of ADEs. In fact, each drug added to a treatment may increase the probability of ADE development by 14%. Although we did not observe the occurrence of ADEs arising from polypharmacy to be higher in elderly people, particular care should be taken with this age group because they are more susceptible to the development of ADEs (17). Varallo et al. (18) demonstrated that the use of several drugs contributed to hospital admission because of DRPs.

Furthermore, polypharmacy increases the chance of prescribing drug interactions. Therefore, simpler pharmacotherapy should be considered by physicians to improve the clinical outcome of the patient, to decrease the rate of noncompliance with treatment due to complex dosing schedules, to contribute to safer pharmacotherapy, and to avoid the misuse and prescription of unnecessary drugs.

Most of the patients reported moderate alcohol intake and use of cardiovascular drugs. Kloner et al. (19) observed that

light-to-moderate intake of alcohol can have beneficial effects on the circulatory system. This finding may explain the lower risk of hospitalization due to an ADE in patients who consumed ethanol, according to the univariate analysis.

### Limitations of the study

The prevalence of hospitalization arising from ADEs may have been overestimated due to 1) the use of a convenience sample; 2) the method of data collection (depending on the memory of the patients and/or their caregivers); 3) a lack of high-quality clinical information (the physicians responsible for prescriptions did not work at the institution, and the patients were poor responders); and 4) the use of the algorithm of Naranjo, which was developed to analyze the safety of drugs in controlled clinical trials. Therefore, the issues addressed by this tool (algorithm) could not all be investigated because of the methodology of the present study.

However, despite its limitations, the present study has scientific relevance, as it portrays a problem that is little known in Brazil and highlights possible difficulties related to the post-marketing surveillance of drugs and causality analyses of ADEs. Moreover, the study demonstrates the need to develop tools which can improve causality assessment of the causal association between the use of drugs and the development of adverse events and to validate tools with higher sensitivity to identify ADEs. It is also necessary to provide continuing education to qualify health professionals to perform pharmacovigilance activities. Moreover, this study fosters discussion regarding the assessment of



health care services provided at the primary and secondary levels to improve patient safety and the awareness of drug takers regarding their pharmacotherapy and health conditions.

Finally, the early detection of ADEs with a high degree of fidelity is of significant interest to health authorities because post-marketing surveillance provides warnings regarding drug safety problems and may trigger actions to reduce the negative outcomes associated with pharmacotherapies. Therefore, pharmacovigilance activities contribute to the rational use of drugs and thus may decrease ADE-related hospital admissions.

Approximately one in two community-dwelling drug takers may be hospitalized due to an ADE. Polypharmacy is a risk factor for the occurrence of ADEs. Data suggest the need to assess the risk/benefit of the prophylactic use of omeprazole and acetylsalicylic acid because these drugs are overprescribed and frequently associated with hospital admissions and negative outcomes. The clinical manifestations of ADEs are nonspecific, which delays treatment, hinders causality analysis, and contributes to the under-reporting of cases.

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## AUTHOR CONTRIBUTIONS

All authors contributed to the development of the project and the manuscript and are aware of its submission.

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